THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

A phase I/II study of venetoclax in combination with azacitidine in relapsed/refractory high-risk myelodysplastic syndrome (MDS) or Chronic Myelomonocytic Leukemia (CMML)
2020-0128

Study Chair: Guillermo Garcia-Manero

_____ _____
Participant's Name Medical Record Number

This is an informed consent and authorization form for a research study. It includes a summary about the study. A more detailed description of procedures and risks is provided after the summary.

This research has been reviewed and approved by an Institutional Review Board (IRB - a committee that reviews research studies).

STUDY SUMMARY

There are 2 parts to this study: Part 1 (dose escalation) and Part 2 (dose expansion).

The goal of Part 1 of this clinical research study is to find the highest tolerable dose of venetoclax that can be given in combination with azacitidine to patients with myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML) that has come back (relapsed) or has not responded to treatment (refractory).

The goal of Part 2 of this study is to learn if the dose of venetoclax found in Part 1 when given with azacitidine can help to control the disease.

This is an investigational study. Venetoclax is FDA approved and commercially available for the treatment of acute myeloid leukemia (AML) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Azacitidine is FDA approved and commercially available for the treatment of MDS. It is considered investigational to give venetoclax in combination with azacitidine to patients with MDS or CMML.

The study doctor can explain how the study drugs are designed to work.

The study drugs may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side effects, potential expenses, and time commitment. If you take part in this study, you may experience side effects, some of which may be severe or fatal.

You can read a list of potential side effects below in the Possible Risks section of this consent.

You may continue receiving the study drugs for as long as the doctor thinks it is in your best interest.

Venetoclax will be provided at no cost to you. You and/or your insurance will be responsible for the cost of azacitidine.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive standard of care treatments outside of this study. You may choose to receive other investigational therapy, if available. The study doctor will discuss the possible risks and benefits of these treatments. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

1. STUDY DETAILS

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. The following screening tests will help the doctor decide if you are eligible:

- You will have a physical exam.
- Blood (about 2 teaspoons) will be drawn for routine tests.
- Bone marrow that was collected from an earlier procedure may be used if collected within 28 days to check the status of the disease and for cytogenetic and genetic mutation tests (tests to look for changes in DNA [the genetic material in cells]). Cytogenetic testing looks at how genetic changes to cells may affect how the disease may react to the study drug. If a sample is not available or was collected more than 28 days before screening, you will have a bone marrow biopsy/aspirate. To collect a bone marrow biopsy/aspirate, an area of the hip or other site is numbed with anesthetic, and a small amount of bone marrow aspirate and bone is withdrawn through a large needle.
- If you can become pregnant, urine or blood (about 1 teaspoon) will be collected for a pregnancy test.

The study doctor will discuss the screening test results with you. If you recently had some tests or procedures, you may not need to have them again. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other options will be discussed with you.

Up to 58 participants will be enrolled in this study. All will take part at MD Anderson.

Study Groups
If you are found to be eligible to take part in this study, you will be assigned to a study group based on when you join this study. Up to 3 groups of 3-6 participants will be enrolled in Part 1 of the study, and up to 40 participants will be enrolled in Part 2.

If you are enrolled in Phase 1, the dose of venetoclax you receive will depend on when you join this study. The first group of participants will receive the lowest dose level of venetoclax. Each new group will receive a higher dose of venetoclax than the group before it, if no intolerable side effects were seen. This will continue until the highest tolerable dose of venetoclax is found.

If you are enrolled in Part 2, you will receive venetoclax at the highest dose that was tolerated in Part 1.

All participants will receive the standard dose of azacitidine.

Study Drug Administration
Each cycle is 4-8 weeks.

You will take venetoclax by mouth every day on Days 1-14 of each cycle. Your venetoclax dosing schedule will depend on when you join the study. Each dose of venetoclax should be taken with a cup (about 8 ounces) of water within 30 minutes after eating (preferably breakfast).

You will receive azacitidine either as an injection under the skin daily or by vein over about 15 minutes on Days 1-5 of each cycle. After Cycle 1, you may be allowed to receive azacitidine at your local oncologist's office, if this is more convenient for you. This will be discussed with you.

You may be admitted to the hospital during the first cycle that you receive venetoclax and azacitidine so the study doctor can watch you for side effects. You will also be given standard drugs to help decrease the risk of side effects. You may ask the study staff for information about how the drugs are given and their risks.

Study Visits
On **Days 1, 2, and 4 of Cycle 1,** blood (about 2 tablespoons) will be drawn for routine tests and to test for signs of tumor lysis syndrome (TLS, a side effect of venetoclax). TLS happens when breakdown products of the cancer cells enter the bloodstream (possibly causing weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage).

On **Day 1 of each cycle**:
- You will have a physical exam.
- Blood (about 2 teaspoons) will be drawn for routine tests.

On **Days 8, 15, and 22 of Cycle 1 and then every 2-4 weeks after that,** blood (about 2 teaspoons) will be drawn for routine tests.

On **Day 28 of Cycles 1, at the end of Cycles 2 and 4, and then every 3-4 cycles after that**, you will have a bone marrow aspiration and/or biopsy to check the status of the disease and for biomarker and genetic mutation/cytogenetic testing. If the study doctor cannot get enough bone marrow, you may be asked to provide additional blood samples (about 4 teaspoons). Biomarkers are found in the blood/tissue and may be related to your reaction to the study drugs.

If the disease gets worse, you may have a bone marrow biopsy/aspirate to check the status of the disease and for biomarker and genetic mutation/cytogenetic testing.

End-of-Study Visit

Within 30 days after your last dose of study drugs, you will come to MD Anderson for an end-of-study visit.

- You will have a physical exam.
- Blood (about 2 teaspoons) will be drawn for routine tests.
- You will have a bone marrow aspiration and/or biopsy to check the status of the disease and for cytogenetic testing.

Follow-Up

After the end-of-study visit, you will be called by the study staff/doctor every 3-6 months for up to 5 years. This call will last about 5-10 minutes. You may be asked to sign a separate consent for this follow-up.

Other Information

While on study, avoid grapefruit, Seville (sour) oranges, and star fruit, including juices and products containing these fruits.

Tell the study doctor/study staff about all medications (including prescription and over-the-counter), herbal remedies, supplements, and vitamins you are taking or plan to take while on study.

2. POSSIBLE RISKS

While on this study, you are at risk for side effects. You should discuss these with the study doctor. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Side effects will vary from person to person, and some may occur after you have stopped receiving treatment. Tell the study staff about any side effects you may have, even if you do not think they are related to the study drugs/procedures.

Venetoclax and azacitidine may each cause a low blood cell count (red, platelets, and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Venetoclax Side Effects

Common (occurring in more than 20% of patients)

• fatigue • diarrhea	• nausea • low blood counts (red, platelets, white)	• upper respiratory tract infection

Occasional (occurring in 3-20% of patients)

• swelling (arm/leg) • fever • headache • abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure)	• vomiting • constipation • back pain • high blood levels of uric acid (possible painful joints and/or kidney failure)	• pneumonia • cough • tumor lysis syndrome (TLS)--breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

TLS is a problem that can occur when cancer cells break down rapidly and the body has to get rid of the broken up cell parts. Sometimes your body, especially the kidneys, cannot remove the cell parts quickly enough, so the level of some of these cell products in your blood, such as salts and acids, can rise. This can happen especially in participants with large tumors or a high number of cancerous white cells in the blood. TLS can lead to serious problems, such as effects on your kidneys and heart (including abnormal heart rhythms), seizures, or even death.

If you develop TLS, your urine may look dark, thick, or cloudy. You may have fever, chills, nausea/vomiting, diarrhea, confusion, shortness of breath, irregular heartbeat, fatigue, muscle pain, joint discomfort, and/or seizure. If you notice any of these, tell your doctor or nurse right away. Your study doctor will closely watch and treat you as needed to lower the risk of any serious changes in your blood or other complications of TLS. You may need to have extra blood tests or EKGs to check for signs of TLS.

You should wear ear plugs or other hearing protection when involved in a loud activity.

If you notice any rash, hives, itching, or other signs of an allergic reaction such as swelling, wheezing, or you are having a hard time breathing, tell your doctor right away.

At this time, there are no known serious side effects that **occur in fewer than 3% of patients**.

Azacitidine Side Effects

The following side effects have been reported when azacitidine is given either by vein or as an injection under the skin:

Common (occurring in more than 20% of patients)

• fever • fatigue/lack of energy • headache • nausea • vomiting	• diarrhea • constipation • loss of appetite • low blood cell counts (red, white, platelets) • weakness	• pain • shivering • cough • difficulty breathing • injection site redness and/or pain

Occasional (occurring in 5-20% of patients)

• chest pain • pale skin • swelling (arm/leg) • abnormal heart sound • fast heartbeat • low blood pressure (possible dizziness/ fainting) • high blood pressure • fainting • dizziness • anxiety • depression • difficulty sleeping • numbness	• low blood levels of potassium (possible weakness /or muscle cramps) • weight loss • abdominal pain, tenderness, and/or swelling • bleeding gums • tongue sores • bleeding in the mouth • mouth blisters and/or sores (possible difficulty swallowing) • upset stomach	• muscle cramps • nosebleed • stuffy and/or runny nose • abnormal breath sounds • wheezing • build-up of fluid around the lungs • lymph node swelling • infection • hardened tissue/inflammation/skin discoloration at the injection site

• hives and/or skin redness • skin bump/sores/rash • dry skin and/or itching • sweating	• hemorrhoids • difficulty swallowing • difficult and/or painful urination • blood in the urine • sore throat	• injection site swelling, itching, and/or rash • increased risk of bleeding after a procedure/surgery • reaction to a blood transfusion

Rare but serious (occurring in fewer than 5% of patients)

• irregular heartbeat • heart failure • bleeding in and/or around the brain • seizures • skin condition with fever and skin lesions • decay of body tissue • lesions due to skin infection • abnormal blood acid/base balance (possible organ damage) • dehydration • gallbladder inflammation (possible abdominal pain) • digestive system bleeding	• tarry stool • enlarged spleen • bone marrow failure • liver failure • kidney failure • build-up of bodily waste products in the blood (possible kidney problems) • coughing up blood • lung inflammation (possible difficulty breathing) • tissue death at the injection site caused by drug leakage • bleeding in the eye • catheter site bleeding • infection at the injection site	• allergic reaction, which may be life-threatening (such as difficulty breathing, low blood pressure, and/or organ failure) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure) • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)

Azacitidine may cause you to develop another type of cancer (such as leukemia, a type of blood cancer).

Using the study drugs together may cause side effects that are not seen when each is given alone. The study drug combination may also increase the frequency and/or severity of the side effects listed above.

Other Risks

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **bone marrow aspirations/biopsies** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the aspiration. An allergic reaction to the anesthetic may occur. A scar may form at the aspiration site.

Although every effort will be made to keep study data safe, there is a chance that your personal health information could be lost or stolen, which may result in a **loss of confidentiality**.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks
Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while on this study. You must use birth control during the study and for at least 3 months after your last dose of study drugs, if you are sexually active.

The study doctor will discuss with you which methods of birth control are acceptable to use.

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant up to 30 days after the last dose of venetoclax, you must tell your doctor right away.

Getting pregnant may result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

Optional Procedure #1: If you agree, extra bone marrow aspirate will be collected from you at screening for biomarker testing. You will not receive the results of this testing.

There are no benefits to you for taking part in the optional procedure. Future patients may benefit from what is learned. You may stop taking part at any time. There will be no cost to you for taking part in the optional procedure.

Optional Procedure Risks

Having **bone marrow aspirations/biopsies** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the aspiration. An allergic reaction to the anesthetic may occur. A scar may form at the aspiration site.

CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES

Circle your choice of “yes” or “no” for each of the following optional

procedures:

Optional Procedure #1: Do you agree to allow extra bone marrow samples to be collected for biomarker testing at screening?

YES **NO**

3. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson or Genentech for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-6477 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

Samples that are collected from you in this study may be used for the development of treatments, devices, new drugs, or patentable procedures that may result in commercial profit.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

Additional Information

4. You may ask the study chair (Dr. Guillermo Garcia-Manero, at 713-745-3428 any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-6477 with any questions that have to do with this study or your rights as a study participant.

5. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety

that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson.

If you withdraw from the study, the study staff may ask if they can continue collecting the results of routine care from your medical record.

6. This study or your participation in it may be changed or stopped without your consent at any time by the study chair, Genentech, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson.

7. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

   Most tests done on samples in research studies are only for research and have no clear meaning for health care. If the research with your identifiable information or samples gives results that do have meaning for your health, the researchers may contact you to let you know what they have found.

8. MD Anderson may benefit from your participation and/or what is learned in this study.

9. This study is sponsored and/or supported by: Genentech.

10. In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s)/supporter. If you have any questions about this, you may call the IRB at 713-792-6477.

Future Research

Data
Your personal information is being collected as part of this study. These data may be used by researchers at MD Anderson and Genentech and/or shared with other researchers and/or institutions for use in future research.

Samples
Samples (such as blood and/or tissue) are being collected from you as part of this study. Researchers at MD Anderson may use any leftover samples that are stored at MD Anderson in future research.

Before being used or shared for future research, every effort will be made to remove your identifying information from any data and/or research samples. If all identifying information is removed, you will not be asked for additional permission before future research is performed.

If you do not want your samples or data to be used for future research, tell the study doctor. You may withdraw your samples at any time by telling your study team. If you decide to withdraw your samples, they will be returned to the lab they came from or destroyed. However, the data and test results already collected from your samples will be kept and may be used.

In some cases, all of your identifying information may not be removed before your data or research samples are used for future research. If future research is performed at MD Anderson, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson before your data and/or research samples can be used. At that time, the IRB will decide whether or not further permission from you is required. The IRB is a committee of doctors, researchers, and community members that is responsible for protecting study participants and making sure all research is safe and ethical.

If this research is not performed at MD Anderson, MD Anderson will not have oversight of any data and/or samples.

Genetic Research
Research samples collected from you as part of this study will be used for genetic research, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment. If genetic research is done with your samples, those who have access to those samples may be able to identify you. The results of this research may also be able to be linked to you.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when deciding to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Nor does this federal law prohibit discrimination based on an already known genetic disease or disorder.

Financial Interest Disclosure
Outside relationships are disclosed to and approved by the Conflict of Interest Committee, which reviews these relationships for compliance with institutional policy. This review helps the IRB to assure that financial relationships do not have an impact

on the conduct of this study. The following members of the study staff have disclosed compensation from the funding source(s) of this study:

- Dr. Guillermo Garcia-Manero (Study Chair)
- Dr. Naval Daver (Co-Investigator)
- Dr. Elias Jabbour (Co-Investigator)

Authorization for Use and Disclosure of Protected Health Information (PHI):

A. During the course of this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:
   - Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
   - The IRB and officials of MD Anderson
   - Genentech, who is a sponsor or supporter of this study, and/or any future sponsors/supporters of the study
   - Study monitors and auditors who verify the accuracy of the information
   - Individuals who put all the study information together in report form

   The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

   Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer at 713-745-6636. If you withdraw your authorization, you will be removed from the study and the data collected about you up to that point can be used and included in data analysis. However, no further information about you will be collected.

E. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____
PRINTED NAME OF PARTICIPANT

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under this protocol.

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE

A witness signature is only required for non-English speakers utilizing the short form consent process (VTPS) and patients who are illiterate.

_____
PRINTED NAME OF WITNESS TO THE VERBAL CONSENT

PERSON OBTAINING CONSENT

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ _____
PERSON OBTAINING CONSENT DATE

_____
PRINTED NAME OF PERSON OBTAINING CONSENT

TRANSLATOR

I have translated the above informed consent as written (without additions or subtractions) into_____and assisted the people
(Name of Language)
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

_____ _____ _____
NAME OF TRANSLATOR SIGNATURE OF TRANSLATOR DATE

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line.)